

# Pancreatic Neuroendocrine Neoplasms: from Genetics to Everolimus Resistance

1. Cell line models of pancreatic neuroendocrine neoplasms (pNEN) are relevant genetic models for different subtypes of pNEN in patients (*this thesis*)
2. The presence of low-abundance mutations in pNEN patient tissue, points towards genetic heterogeneity in pNEN (*this thesis*).
3. Everolimus resistance in pNEN can be overcome by combined PI3K-mTOR inhibition (*this thesis*)
4. Cell cycle proteins are involved in everolimus resistance and might be an interesting therapeutic target (*this thesis*)
5. Everolimus resistance in pNEN might be mediated by cross-talk with MAPK-ERK pathway and adding ERK inhibition to mTOR inhibition might overcome everolimus resistance (*this thesis*)
6. The development of intratumor heterogeneity poses major limits to the potential targeting of mutated pathways on the basis of molecular analysis of a tumor sample (i.e., limits to the central concept of personalized medicine) (*Tannock and Hickman, N Engl J Med, 2016, 375 (13), 1289-94*)
7. Many actionable molecular alterations occur in 3% or less of patients with refractory malignancies (*Flaherty et al, JNCI: Journal of the National Cancer Institute, 2020, 112(10):1021-1029.*)
8. Selective reporting of positive preclinical or observational research is a potential explanation for why the reported results of only 11–25% of promising preclinical studies can be independently replicated for drug development, why clinical trials often do not confirm the benefit shown in previous reports of animal or clinical studies and why many reported studies showing new epidemiological and genetic associations are subsequently refuted (*Chan et al, Lancet, 2014, 383(9913):257-66.*)
9. At the level of the individual the right decision is fundamentally under-determined by the results of a trial. Even in retrospect, it is usually impossible to tell whether the right decision was made for any individual patient (*Kent et al, BMJ. 2018;363:k4245*)
10. Whatever the extent of future progress, evidence-based medicine's success in providing a framework for fully integrating research evidence into the delivery of health care, and raising awareness of the need for consideration of individual patient values and preferences, will remain enduring contributions to clinical medicine and related fields (*Djulbegovic & Guyatt, Lancet, 2017, 390(10092):415-423.*)
11. The measure of any society is how it treats its women and girls (*Michelle Obama*)